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Atty Dkt.: 620-149
Date: April 23, 2004

To: Examiner YU, M. - Group: 1642
Firm: USPTO
Facsimile No.: (703) 872-9306
From: B. J. Sadoff

Number of Pages (including cover sheet): 16

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(typed) B. J. Sadoff

ATTACHMENT/S: **OFFICIAL AMENDMENT UNDER RULE 116 AND DECLARATION**

MESSAGE:

In re PATENT APPLICATION OF:

Nixon & Vanderhye P.C.
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Meeyl. W. Ison
(for) B. J. Sadoff

ATTACHMENT/S: **OFFICIAL AMENDMENT UNDER RULE 116 AND DECLARATION**

MESSAGE:

In re PATENT APPLICATION OF:

LA THANGUE et al
Serial No.: 09/900,147
Filed: July 9, 2001
For: PEPTIDE ANTAGONISTS OF DP TRANSCRIPTION FACTORS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RESPONSE UNDER RULE 116
EXPEDITED HANDLING PROCEDURES

In re Patent Application of Atty Dkt. 620-149
C# M#
LA THANGUE et al TC/A.U. 1642
Serial No. 09/900,147 Examiner: YU, M.
Filed: July 9, 2001 Date: April 23, 2004
Title: PEPTIDE ANTAGONISTS OF DP TRANSCRIPTION FACTORS

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **0** minus highest number previously paid for **20** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **0** minus highest number previously paid for **3** (at least 3) = 0 x $ 86.00	$	0.00
If proper multiple dependent claims now added for first time, add $290.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $420.00/2 months; $950.00/3 months)	$	0.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($770.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**0.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☐ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	0.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00)	$	0.00
Other:		**0.00**
TOTAL FEE ENCLOSED	$	**0.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663 Reg No 32955

Signature: Mary d. Wilson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

LA THANGUE et al — Atty. Ref.: 620-149; Confirmation No. 4292

Appl. No. 09/900,147 — TC/A.U. 1642

Filed: July 9, 2001 — Examiner: YU, M.

For: PEPTIDE ANTAGONISTS OF DP TRANSCRIPTION FACTORS

* * * * * * * * * * *

April 23, 2004

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT UNDER RULE 116

This is in response to the Office Action dated February 23, 2004, in the above matter. Kindly amend this application as follows.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-20 (Canceled).

21. (Currently Amended) A polypeptide consisting ~~essentially~~ of:

(i) a sequence corresponding to residues 163 to 199 of DP-1, said sequence being: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1); or

(ii) a sequence corresponding to residues 163-199 of DP-1, said sequence being: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1), and said sequence further including from 1 to 5 amino acid residues at the N- or C-terminus thereof, where the presence of such residues has no significant effect on the function of the polypeptide.

22. (Currently Amended) A ~~polypeptide~~ fragment of a ~~the~~ polypeptide consisting ~~essentially~~ of:

(i) the sequence: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1), or

(ii) the sequence: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1), said sequence further including from 1 to 5 amino acid residues at the N- or C-terminus thereof, where the presence of such residues has no significant effect on the function of the polypeptide;

which fragment is capable of antagonising the heterodimerisation of a DP protein with an E2F protein.

23. (Currently Amended) A ~~polypeptide~~ fragment according to claim 22 which comprises the sequence NVLMAMNII (SEQ ID NO:2) or ALNVLMA (SEQ ID NO:7).

24. (Currently Amended) A ~~polypeptide~~ fragment according to claim 23 which is selected from the group consisting of:

RRRVYDALNVLMAMNIISK (SEQ ID NO:3);

NVLMAMNIISKEKKEIKWIG (SEQ ID NO:4);

RVYDALNVLMAMNIIS (SEQ ID NO:5); and

YDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:6).

25. (Currently Amended) A variant of a polypeptide consisting ~~essentially~~ of:

(i) a sequence corresponding to residues 163 to 199 of DP-1, said sequence being: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1), or

(ii) a sequence corresponding to residues 163 to 199 of DP-1, said sequence being: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1), and said sequence further including from 1 to 5 amino acid residues at the N- or C-terminus thereof, where the presence of such residues has no significant effect on the function of the polypeptide;

said variant differing from the polypeptide by the presence of from 1 to 5 amino acid substitutions in the sequence of said polypeptide, said variant being capable of antagonising the heterodimerisation of a DP protein with an E2F protein.

26. (Previously Presented) A variant according to claim 25 wherein the substitutions include substitutions selected from one or more residues corresponding to residues 167, 169, 171 and 175 of DP-1.

27. (Currently Amended) A polypeptide which comprises:

(i) a first portion having an amino acid sequence selected from the group consisting of:

(a) KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1),

(b) NVLMAMNII (SEQ ID NO:2),

(c) RRRVYDALNVLMAMNIISK (SEQ ID NO:3),

(d) NVLMAMNIISKEKKEIKWIG (SEQ ID NO:4),

(e) RVYDALNVLMAMNIIS (SEQ ID NO:5),

(f) YDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:6), and

(g) ALNVLMA (SEQ ID NO:7); and

(ii) a second portion, attached to the N- or C-terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion in DP-1.

28. (Previously Presented) A polypeptide according to claim 27 wherein the second portion is a membrane translocation sequence.

29. (Previously Presented) A polypeptide according to claim 28 wherein the membrane translocation sequence is the membrane translocation sequence of the *Drosophila melanogaster* antennapedia protein.

30. (Currently Amended) A ~~pharmaceutical~~ composition comprising a polypeptide according to any one of claims 21 to 29 together with a pharmaceutically acceptable diluent or carrier.

31. (Currently Amended) A ~~pharmaceutical~~ composition according to claim 30 which further comprises a cytostatic or cytotoxic agent.

32. (Previously Presented) A composition formulation comprising a polypeptide of SEQ ID NO:1 in the form of an orally, topically or parenteraly administrable form.

33. (Withdrawn) A method of inducing apoptosis in a cell which comprises introducing into said cell an effective amount of a polypeptide according to claim 21.

34. (Withdrawn) A method according to claim 33 wherein said cell is a tumour cell.

35. (Withdrawn) A method according to claim 33 wherein said cell is a cardiovascular cell.

36. (Currently Amended) A product comprising a polypeptide consisting ~~essentially~~ of:

(i) a sequence corresponding to residues 163 to 199 of DP-1, said sequence being: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1), or

(ii) a sequence corresponding to residues 163 to 199 of DP-1, said sequence being: KNIRRRVYDALNVLMAMNIISKEKKEIKWIGLPTNSA (SEQ ID NO:1), and said sequence further including from 1 to 5 amino acid residues at the N- or C-

terminus thereof, where the presence of such residues has no significant effect on the function of the polypeptide;

and a cytostatic or cytotoxic agent as a combined preparation.

37. (Withdrawn) A method of treating uncontrolled proliferation of cells in a human or animal body in need of said treating comprising administering a composition of claim 31 to said human or animal body such that said uncontrolled proliferation of cells is treated.

REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The Examiner's Summary of the March 1, 2004 interview indicates claims 28 and 29 are objected to as being dependent on a rejected base claim. This is not correct. Claim 29 depends from claim 28 which in turn depends from independent claim 27. No rejection of claim 27 is found in the Action. According, claims 27-29 should be indicated as allowable. Further comments regarding the substance of the March 1, 2004 interview are set forth in the Request filed March 2, 2004.

Claims 33-35 and 37 presently stand withdrawn from consideration. These method claims depend from elected product claims and it is submitted that rejoinder of these claims after allowance of the product claims will be in order and same is again requested. In view of this request, the claims have not been cancelled.

As regards the Examiner's objection to the drawings and drawing corrections set forth on pages 2-4 of the Action, attention is directed to the fact that the peptides of Figure 1 which are shown in Figure 3 include an additional tag which is a peptide containing 16 amino acid residues taken from the third helix of the antennapedia homeodomain protein, as noted on page 27, lines 9-31, of the subject specification. Page 28, lines 3-6, for example, makes clear that the asterisk (*) after the noted peptide name indicates the inclusion of the tag. Further, page 29, lines 17-20, for example, makes clear that the result of the tagged peptides are shown in Figure 3. It is submitted

that these comments constitute an explanation for the changes and previous amendment to the figures and an explanation for the differences in labels of the peptides between Figures 1 and 3.

Claims 30 and 31 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

It appears that this rejection is based, at least in part, on an alleged "failure" to provide any *in vivo* model data. Submitted herewith is a Declaration that sets out an experiment in mice that evidences the *in vivo* effectiveness of the compound of the invention.

The Examiner refers to the parent USP 6,268,334 in the rejection and suggests that there is a difference between the "pharmaceutically acceptable carrier" of claim 1 of that patent and the "pharmaceutical" of the present invention. While basis for this assertion is not seen, the term "pharmaceutical" has been removed from claims.

In view of the above, reconsideration is requested.

Claims 21-24, 32 and 36 stand rejected under 35 USC 102(e) as allegedly being anticipated by USP 5,863,757. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The claims as now presented read "consisting of" rather than "consisting essentially of". Furthermore, the instant claims specify that SEQ ID NO:1 can contain from 1 to 5 additional amino acids only and that those amino acids must be at either the

N- or C-terminal of the polypeptide of SEQ ID NO:1. The polypeptide of SEQ ID NO:1 either with or without the 1 to 5 additional amino acids at the specific locations recited is not taught by the cited art. Accordingly, reconsideration is requested.

Claim 25 stands rejected under 35 USC 102(e) as allegedly being anticipated by USP 5,859,199. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The Examiner contends that the citation discloses a sequence similar to that of SEQ ID NO:1 of the present invention but which sequence has one amino acid difference at position 163 of SEQ ID NO:1 and is smaller than SEQ ID NO:1. The above-noted revision of claim 25 moots the rejection and reconsideration is requested.

Claims 23 and 24 stand rejected under 35 USC 112, second paragraph. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of the claims to read "A fragment" rather than "A polypeptide fragment". Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C. Reg No 32,955

By: Mary J. Wilson
(for) B. J. Sadoff
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DECLARATION

I declare that I am PROFESSOR ROBERT BROWN, Director of Laboratory Research Medical Oncology of CR-UK Beatson Laboratories, Garscube Estate, Glasgow, G61 1BD, UK.

I furthermore declare that I was tasked by the assignee, Prolifix Limited, of US Patent Application Serial Number 09/900,147 in the name of La Thangue et al., and filed on July 9, 2001, to design and oversee an experiment to determine the effects of E2F peptides *in vivo* on tumour take, the results of which experiment address the objections by Examiner Yu in the Office Action of February 23, 2004 under 35 USC s112 to the failure of claims 30 and 31 currently on file to comply with the enablement requirements by demonstrating using an *in vivo* model that the polypeptide of the invention is effective in the inhibition of tumour take.

The experiment and the results obtained were performed as follows:

Effects of E2F peptides on tumour take.

To investigate whether the E2F peptides have an effect on in vivo tumour take in a mouse model, the following experiments were performed. A2780 ovarian cancer cells were exposed to H2" peptide (antennapedia tagged SEQ ID NO:3) (working solution of 30 μM) and rotated for 3hrs at 37 C before being injected subcutaneously into the flanks of athymic nude mice. The antennapedia uptake sequence alone (ANT) and the uptake sequence linked to a scrambled H2 sequence (AHS2) were used as negative controls. Cells were injected at a concentration of 10^7 cells in 100 μl per injection site, two sites per mouse. Tumour number and size were recorded at day 10.

Results:

Treatment	Average tumour size	Tumour formation
ANT	8x12mm	12/12
AHS2	9x9mm	12/12
H2"	6x6mm	2/12

To examine the effect of cell number on tumour formation, cells were exposed to peptide as previously described and injected into mice at a concentration of 10^6 cells per injection site. Tumour size and number were recorded at day 15. There were five mice in each of two groups.

Results:

Treatment	Average tumour size	Tumour formation
AHS2	9x9mm	7/10
H2*	6x6mm	3/10

Thus it is apparent that the peptide specifically inhibits tumour take in this mouse model, at 10^6 and 10^7 tumour cells injected.

Signed .....

Witnessed .....

Date 22/4/04